

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(51) International Patent Classification<sup>7</sup>: C07C

GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(21) International Application Number:

PCT/EP2003/006416

(74) Agent: LEAROYD, Stephanie, Anne; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(22) International Filing Date: 18 June 2003 (18.06.2003)

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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(30) Priority Data: 0214254.5 20 June 2002 (20.06.2002) GB

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(72) Inventors; and

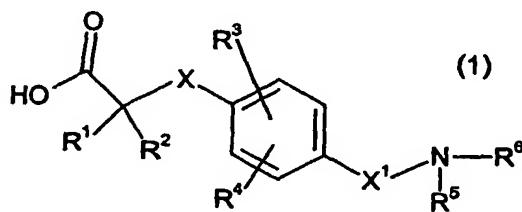
(75) Inventors/Applicants (for US only): BESWICK, Paul, John [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). HARLING, John, David [GB/GB]; GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW (GB). KLEANTHOUS, Savvas [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). PATEL, Vipulkumar, Kantibhai [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). SIMPSON, Juliet [GB/GB];

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— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CHEMICAL COMPOUNDS



wherein the phenyl or heteroaryl group is optionally substituted with 1, 2 or 3 moieties selected from the group consisting of C1-6 alkyl, halogen, -OC1-6 alkyl, -SO2C1-3 alkyl, phenyl (optionally substituted by one or more groups selected from halogen, CF3, C1-3 alkyl, OC1-3 alkyl, acetyl, CN).

(57) Abstract: A compound of formula (1) or a pharmaceutically acceptable salt, solvate, or hydrolysable ester thereof. Wherein: R1 and R2 are independently hydrogen or C1-3 alkyl; X represents a bond, CH2 or O; R3 and R4 are independently hydrogen, C1-6 alkyl, OCH3, CF3, allyl or halogen; X1 is CH2, SO2, or CO; R5 is -C1-6 alkyl (optionally substituted by C1-6alkoxy or C1-6alkylthio), -C2-6 alkenyl, -CO-6 alkyl phenyl (wherein the phenyl is optionally substituted by one or more CF3, halogen, C1-3 alkyl, C1-3 alkoxy, -COCl-6 alkyl, SO2C1-6 alkyl; R6 is phenyl or a 6 membered heteroaryl group containing 1,2 or 3 N atoms

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GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

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(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

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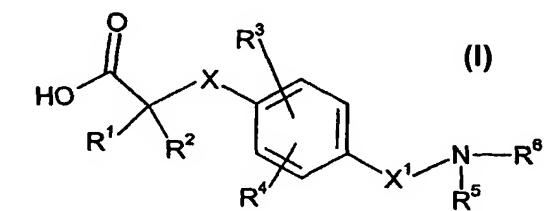
— with international search report

(72) Inventors; and  
(75) Inventors/Applicants (for US only): BESWICK, Paul, John [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). HARLING, John, David [GB/GB]; GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW (GB). KLEANTHOUS, Savvas [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). PATEL, Vipulkumar, Kantibhai [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). SIMPSON, Juliet [GB/GB];

(88) Date of publication of the international search report: 14 October 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROPIONIC ACID DERIVATIVES AND THEIR USE AS HPPARS ACTIVATORS



(57) Abstract: A compound of formula (I) or a pharmaceutically acceptable salt, solvate, or hydrolysable ester thereof. Wherein: R1 and R2 are independently hydrogen or C1-3 alkyl; X represents a bond, CH2 or O; R3 and R4 are independently hydrogen, C1-6 alkyl, OCH3, CF3, allyl or halogen; X1 is CH2, SO2, or CO; R5 is -C1-6 alkyl (optionally substituted by C1-6 alkoxy or C1-6 alkylthio), -C2-6 alkenyl, -C0-6 alkyl phenyl (wherein the phenyl is optionally substituted by one or more CF3, halogen, C1-3 alkyl, C1-3 alkoxy), -COC1-6 alkyl, SO2C1-6 alkyl; R6 is phenyl or a 6 membered heteroaryl group containing 1, 2 or 3 N atoms wherein the phenyl or heteroaryl group is optionally substituted with 1, 2 or 3 moieties selected from the group consisting of C1-6 alkyl, halogen, -OC1-6 alkyl, -SO2C1-6 alkyl, alkyl, phenyl (optionally substituted by one or more groups selected from halogen, CF3, C1-3 alkyl, OC1-3 alkyl, acetyl, CN).

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optionally substituted with 1, 2 or 3 moieties selected from the group consisting of C1-6 alkyl, halogen, -OC1-6 alkyl, -SO2C1-6 alkyl, alkyl, phenyl (optionally substituted by one or more groups selected from halogen, CF3, C1-3 alkyl, OC1-3 alkyl, acetyl, CN).

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/06416

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C217/58 C07D213/74 C07D213/75 C07D239/42 C07D241/20  
 C07C311/29 A61K31/33 A61K31/18 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 273 518 A (FUJISAWA PHARMACEUTICAL CO) 2 January 1976 (1976-01-02) page 1, l. 1-3; page 2, l. 31-37; page 31, compounds 18, 19; page 42, compounds 2, 3; example 6(c); example 6(d); claims -----	1-6,9, 11,14-17
A	WO 02/28821 A (PERNERSTORFER JOSEF ;WOLTERING MICHAEL (DE); URBANNS KLAUS (DE); B) 11 April 2002 (2002-04-11) abstract; claims 1-16; examples 1-11,1-12,1-13,1-14 -----	1-17
A	EP 1 067 109 A (ONO PHARMACEUTICAL CO) 10 January 2001 (2001-01-10) claims 1-8 ----- -----	1-17
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

31 October 2003

Date of mailing of the international search report

09.01.2004

Name and mailing address of the ISA

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Authorized officer

Rufet, J

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/06416

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/23407 A (GLAXO GROUP LTD ;OPLINGER JEFFREY ALAN (US); STUART LUDWIG WILLIAM) 27 April 2000 (2000-04-27) the whole document -----	1-17
A	US 3 912 756 A (WOLFF HANS PETER ET AL) 14 October 1975 (1975-10-14) claims 1-10; example 11 -----	1-16

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/06416

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**Although claims 18 and 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8 in part, 9 completely, 10-17 in part

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8 partially, 9 completely, 10-17 partially

Provision of compounds of formula (I) according to claim 1 wherein X1 is -CH2- useful for the manufacture of a medicament for treating or preventing dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia and anorexia nervosa, which are PPAR mediated diseases or conditions.

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2. claims: 1-8, 10-17 all partially

Provision of compounds of formula (I) according to claim 1 wherein X1 is -SO2- useful for the manufacture of a medicament for treating or preventing dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia and anorexia nervosa, which are PPAR mediated diseases or conditions.

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3. claims: 1-8, 10-17 all partially

Provision of compounds of formula (I) according to claim 1 wherein X1 is -CO- useful for the manufacture of a medicament for treating or preventing dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia and anorexia nervosa, which are PPAR mediated diseases or conditions.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/06416

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FR 2273518	A 02-01-1976	JP 1254416 C JP 51125229 A JP 59029575 B JP 1254417 C JP 51125230 A JP 59029576 B JP 1254425 C JP 51100033 A JP 59029577 B JP 1254426 C JP 51101938 A JP 59029578 B JP 1308351 C JP 51101977 A JP 60025425 B JP 1254427 C JP 51101939 A JP 59029579 B JP 1254428 C JP 51105022 A JP 59029580 B JP 1228417 C JP 50154214 A JP 59003465 B JP 1228418 C JP 50157325 A JP 59003466 B JP 50157326 A AT 351517 B AT 125378 A AU 8185575 A CA 1050985 A1 CH 613940 A5 DE 2524865 A1 DK 248875 A ES 438236 A1 ES 454644 A1 FR 2273518 A1 GB 1503953 A SE 7506335 A AT 354423 B AT 424575 A AT 352705 B AT 125178 A ES 454643 A1 AT 355009 B AT 125278 A BE 829791 A1 NL 7506611 A ZA 7503607 A	12-03-1985 01-11-1976 21-07-1984 12-03-1985 01-11-1976 21-07-1984 12-03-1985 03-09-1976 21-07-1984 12-03-1985 08-09-1976 21-07-1984 26-03-1986 08-09-1976 18-06-1985 12-03-1985 08-09-1976 21-07-1984 12-03-1985 17-09-1976 21-07-1984 19-09-1984 12-12-1975 24-01-1984 19-09-1984 19-12-1975 24-01-1984 19-12-1975 25-07-1979 15-01-1979 09-12-1976 20-03-1979 31-10-1979 02-01-1976 05-12-1975 16-05-1977 01-12-1978 02-01-1976 15-03-1978 05-12-1975 10-01-1979 15-06-1979 10-10-1979 15-03-1979 01-06-1979 11-02-1980 15-07-1979 01-10-1975 08-12-1975 29-09-1976
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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

R/EP 03/06416

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